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Case Report

Image Characteristics of Muscular Sarcoidosis and Muscular Lymphoma: Report of Two Cases with Comparison between them

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Abstract.

The association between sarcoidosis and lymphoproliferative diseases is well-recognized. As fluorine-18 fluorodeoxyglucose (FDG)-positron emission tomography (PET) is increasingly utilized in lymphoma staging, it is important for clinicians to be aware of lymphoma mimickers on FDG-PET. Here we describe two patients with diffuse large B-cell lymphoma who presented with high muscular FDG-uptake. The first patient had histologically proven concomitant muscular sarcoidosis, while the second patient had primary skeletal muscle lymphoma. FDG-PET is of limited utility in discerning sarcoidosis and lymphoma, as both lesions are FDG-avid. Magnetic resonance imaging may provide clues to differentiate these two entities non-invasively. The "3 stripes" and "dark star" signs are characteristic for muscular sarcoidosis, whereas muscular lymphoma usually demonstrates homogenous gadolinium enhancement. Nevertheless, histological examination remains the gold standard in distinguishing hese two diseases. In conclusion, while FDG-PET may be useful in monitoring disease extent and activity of both sarcoidosis and lymphoma, and MRI may provide additional diagnostic information, biopsy is still recommended when clinical decision-making dictates confirmatory diagnosis.

Keywords **:** lymphoma, sarcoidosis, PET, MRI

病例報告

肌肉型類肉瘤症與原發性肌肉淋巴瘤：兩病例之比較報告

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中文摘要

近年來，正子掃描廣泛用於淋巴瘤的分期檢查。因此，與淋巴瘤在正子掃瞄上有相似表現的疾病，可能會造成臨床分期的錯誤，進而影響治療策略。過去已有文獻報導淋巴瘤與類肉瘤症並存的案例，稱為類肉瘤—淋巴瘤症候群。本文描述兩位患有瀰漫性大 B 細胞淋巴瘤的病人，在正子掃描下，其骨骼肌均表現高葡萄糖吸收量。第一位病人診斷為淋巴瘤，肌肉病灶經切片後，證實為合併肌肉型類肉瘤症；第二位病人則是原發性肌

肉淋巴瘤。核磁共振攝影可用以協助區辨肌肉型類肉瘤症與原發性肌肉淋巴瘤：典型的肌肉型類肉瘤症在核磁共振上表現「三斑」與「暗星」徵象，原發性肌肉淋巴瘤則表現均勻的高顯影劑顯影。雖然核磁共振掃瞄可輔助鑑別診斷，但組織學檢查仍為區辨標準。在治療類肉瘤症與淋巴瘤的病人，正子掃瞄可用以評估疾病範圍與活性，核磁共振可提供額外的診斷資訊，但當病人的治療計劃會因診斷而改變時，仍應進行組織切片做確切的區辨。

關鍵字: 淋巴瘤、類肉瘤症、正子掃描、核磁共振

INTRODUCTION

There is growing evidence demonstrating the association between sarcoidosis and lymphoproliferative diseases [1,2]. The coexistence of sarcoidosis and lymphoma, the "sarcoidosis-lymphoma syndrome", is difficult to diagnose because of overlapping clinical and radiological features [1]. Both sarcoidosis and lymphoma show fluorine-18 fluorodeoxyglucose (FDG)-avid lesions in positron emission tomography (PET) [2]. PET has gained an increasingly important role in the staging and follow-up of lymphoma. On the other hand, PET has been utilized to monitor disease activity and to follow treatment response in sarcoidosis [3]. It is highly possible to mistake sarcoid lesions for lymphoma, or vice versa, on FDG-PET alone. Here we present two cases of lymphoma with high muscular FDG uptake due to distinct etiology. The first patient was diagnosed to have diffuse large B-cell lymphoma (DLBCL) of the nasopharynx concurrently with histologically proven muscular sarcoidosis, whereas the second patient had primary skeletal muscle DLBCL. The radiological similarity of muscular sarcoidosis and muscular lymphoma is described and the possible means to differentiate these two disease entities are discussed.

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CASE REPORTS

Case 1

A 63-year-old woman visited our hospital for evaluation of an enlarging right neck mass noted for 3 months. She has no underlying diseases except for multinodular goiter. She reported no fever, night sweats, nasal obstruction, or epistaxis, but her body weight decreased from 52 kilograms to 44 kilograms in 5 months. Head and neck MRI showed bilateral cervical lymphadenopathy, with the largest right level II lymph node measuring 3.5 cm, as well as thickened left nasopharyngeal mucosa. Nasopharyngeal biopsy revealed diffuse large B-cell lymphoma (DLBCL), positive for CD20. A PET scan demonstrated an intensive FDG uptake in the nasopharynx and bilateral enlargement of cervical lymph nodes (SUVmax=14.1), mild to moderate hot spots in hilar nodes and lungs on both sides (SUVmax = 4.0), and patchy linear foci of mild to moderately increased metabolism in the muscles of upper and lower extremities of both sides, trunk, and buttock (SUVmax=7.8) (Figure 1A).

Because the patchy FDG-avid muscular lesions are unusual for lymphoma, further investigation was arranged. The muscular lesions could not be palpated on physical examination and the patient reported no myalgia or weakness. The creatinine kinase level was 25 U/L (reference 30-223 U/L). MRI of both lower extremities detected numerous intramsucular lesions in parallel with muscle fibers. These lesions were isointense on T1-weighted images and hyperintense on T2-weighted images, and showed rim gadolinium enhancement with dark-star centers (Figure 1B-D).

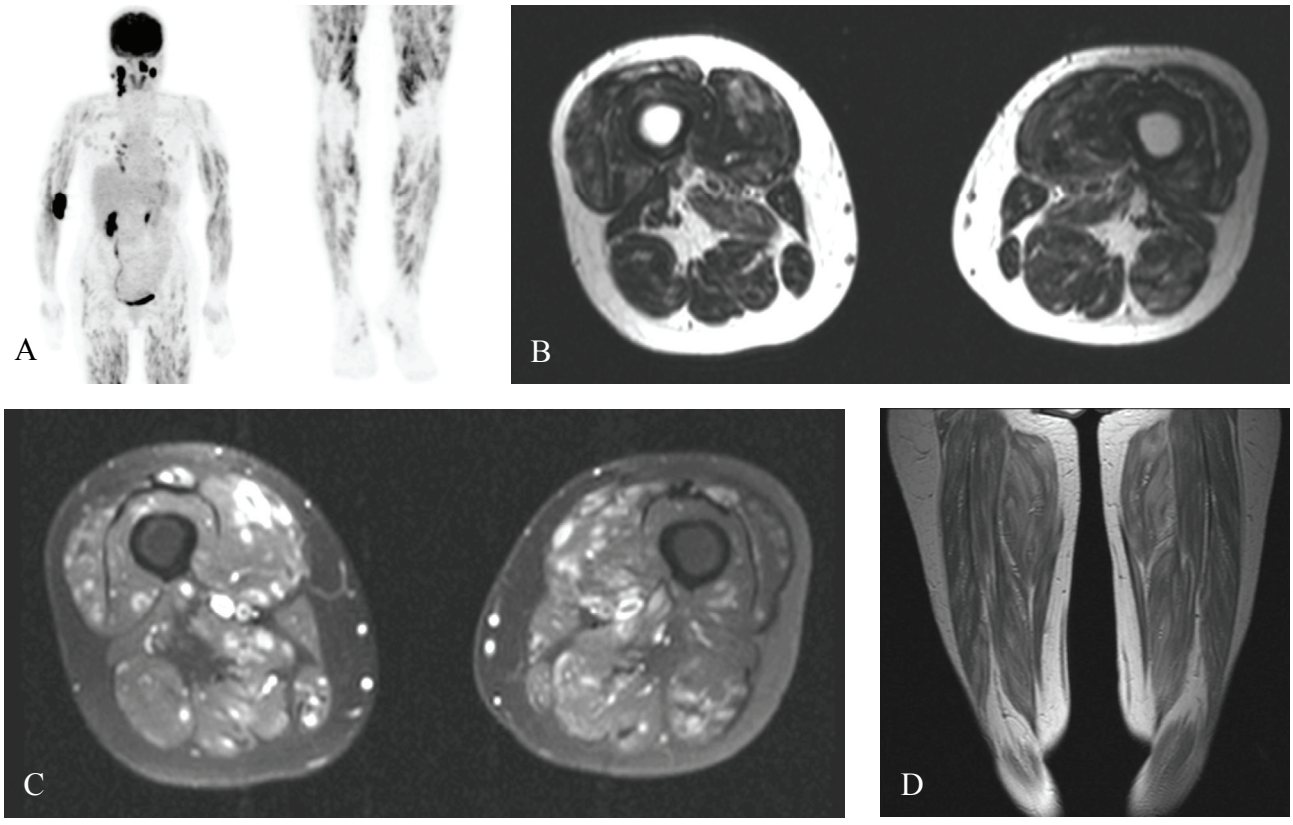

Figure 1. Images of Case 1. (A) FDG-PET in maximal intensity projection mode. In addition to the intense FDG uptake at the nasopharynx and bilateral cervical lymph node involvement illustrating lymphoma extent, the characteristic linear "tiger man" uptake pattern of muscular sarcoidosis in the striated muscles of the extremities. (B) T2-weighted axial MR image at the level of mid thigh. There were numerous hyperintense intramuscular lesions. (C) gadolinium (Gd)-enhanced T1-weighted axial image with fat-saturation at the same level, showing rim enhancement and a central "dark star" sign, which manifests as a "3 stripes" sign (i.e. a central low signal stripe sandwiched by two outer parallel stripes of contrast enhancement) on (D) Gd-enhanced T1-weighted coronal image

Muscle biopsy of the left thigh showed non-caseating granulomatous inflammation composed of aggregates of tightly clustered epithelioid cells and giant cells (Figure 2). Staining for acid-fast bacilli was negative, and thus the lesion was compatible with sarcoidosis. The final diagnosis was DLBCL involving the nasopharynx and cervical lymph nodes, stage IIB, with concomitant pulmonary and muscular sarcoidosis. The patient underwent R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone) chemotherapy uneventfully.

Case 2

A 65-year-old man visited to our hospital with progressive left thigh swelling for 3 months. He reported no fever, weight loss, or night sweats. Physical examination revealed swelling of the left medial thigh. MRI of the lower extremities revealed an enlarged left tensor fasciae latae and hamstring muscles, with isointensity on T1-weighted images and hyperintensity on T2-weighted images (Figure 3B-C). There was mild contrast enhancement after gadolinium administration (Figure 3D). CT-guided biopsy of the left thigh mass revealed histologically a DLBCL with a

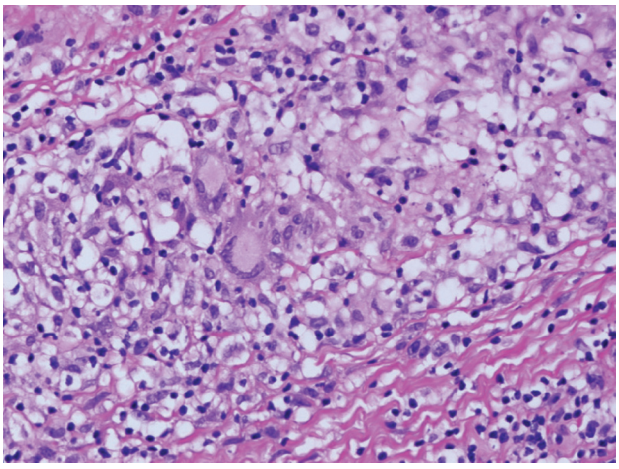

Figure 2. Hematoxylin-eosin staining (400X) showsing non-caseating granulomatous inflammation composed of epithelioid cells and giant cells in a background of fibrous tissue

positive stain for CD20. FDG-PET scan showed a large focal hot area in the left pelvic wall and left thigh muscle (SUVmax=14.31; image not shown). The diagnosis was primary skeletal muscle DLBCL, stage IVE, with extensive muscular involvement. The patient underwent six courses of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, dexamethasone) chemotherapy, but obtained only partial response. The disease subsequently progressed to involve the brain, nuchal muscles, and pelvic cavity (Figure 2A). Salvage chemotherapy comprising of R-ICE (rituximab, ifosfamide, cisplatin, and etoposide) was administered. He developed, however, status epilepticus secondary to extensive brain metastasis and subsequently died of sepsis 7 months after the initial diagnosis.

DISCUSSION

The association between sarcoidosis and lymphoma has been well described in the pliterature [1,2,4]. Sarcoid patients have a 5.5 fold increase in risk of developing malignant lymphoproliferative diseases [1]. Both Hodgkin's lymphoma and non-Hodgkin's lymphoma have been found in patients with sarcoidosis, and lymphoma of the T-cell lineage has been reported as well [2,4]. The mechanism underlying this association remains unclear, but immune dysregulation is the most prevailing hypothesis [4].

In sarcoidosis, myopathy occurs in 50 to 80% of patients, while only 1.4% are symptomatic [5,6]. Symptomatic sarcoid myopathy is classified into three forms, namely, chronic myopathy, acute myositis, and lesions of nodular type [6-8]. In our first case, the patient's sarcoid myopathy was entirely asymptomatic, and was only an incidental finding during staging workup for lymphoma. For symptomatic sarcoid myopathy, a steroid is the mainstay of treatment [7,9].

Primary skeletal muscular lymphoma is a rare disease, predominantly involving the lower extremities. Muscular involvement of lymphoma may develop through three different mechanisms. Most commonly it is caused by hematogenous or lymphatic dissemination. It can also occur via direct extension from adjacent structures such as bone or lymph nodes. The third pathway, as a primary extranodal disease, is the rarest, accounting for only 0.5% of all extranodal lymphomas [10]. The clinical manifestation of muscular lymphoma is enlargement of the involved muscles, associated with or without pain. The most common site of muscular involvement is the lower extremity, representing 50% of cases. Treatment generally consists of chemotherapy with or without adjuvant radiotherapy [11]. In our second case, the patient developed primary skeletal muscle lymphoma of the thigh, which initially responded to first line chemotherapy but rapidly recurred with dissemination to the central nervous system. Data on the prognosis of muscular lymphoma are sparse due to its rare occurrence, but the prognosis has generally been regarded poor [11].

Both sarcoidosis and lymphoma are 18F-FDG-avid on PET. Our first patient's thick linear FDG uptake predominantly involved the lower extremity muscles, which was consistent with the "tiger man sign" designated for the PET pattern of sarcoid myopathy [12,13]. In contrast, the FDG uptake of muscu-

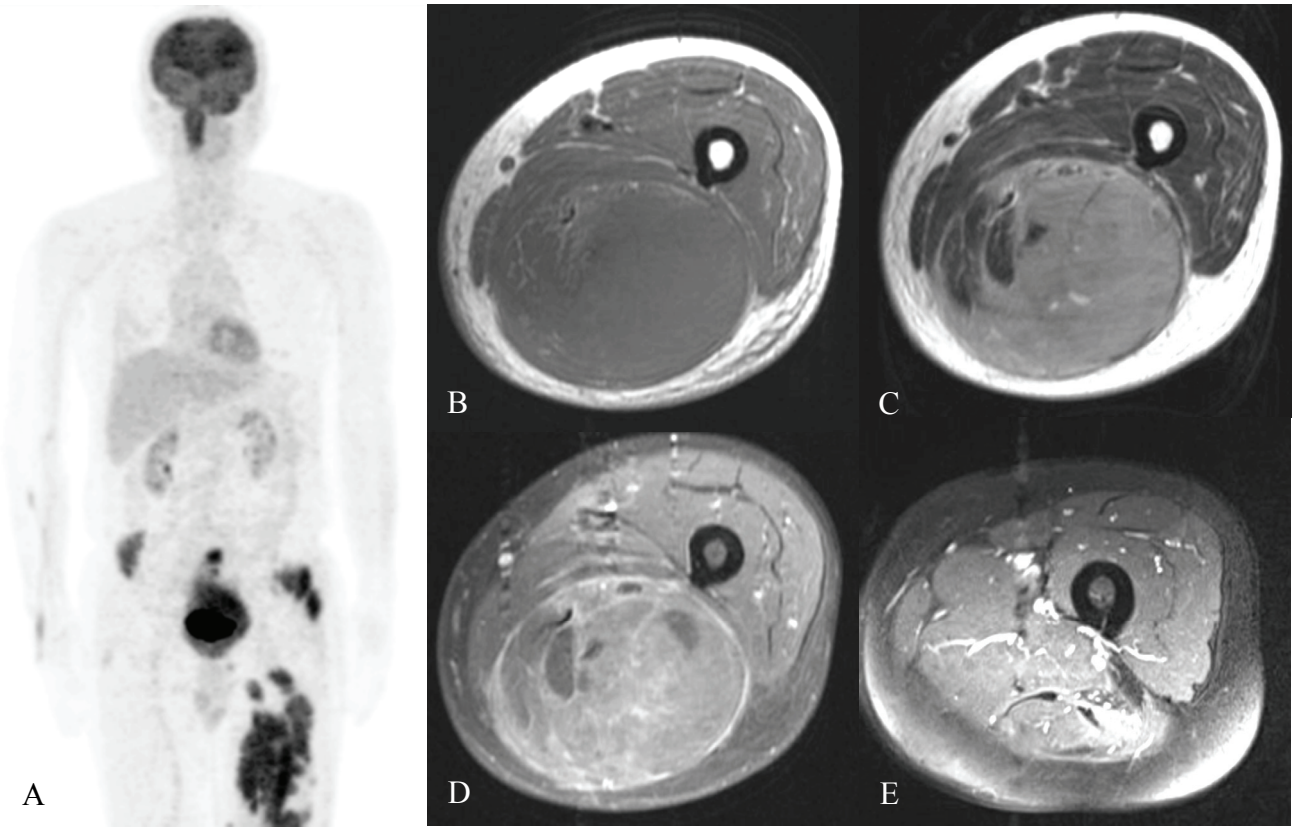

Figure 3. Images of Case 2. (A) FDG-PET in maximal intensity projection mode, showing nodular intense hypermetabolic areas involving the left thigh, pelvic cavity, and right nuchal muscles. (B) T1-weighted axial MR image at the level of mid thigh, showing isointense left hamstring muscular enlargement. (C) T2-weight image at the same level. The involved muscles showed hyperintensity. (D) Gd-enhanced T1-weighted image with fat-saturation, showing mild homogeneous contrast enhancement. (E) Gd-enhanced T1-weighted image with fat-saturation after six courses of R-CHOP chemotherapy, showing resolved intramuscular mass with faint traces of contrast enhancement

lar lymphoma is intense and homogenous in our second patient. Differentiating sarcoid lesions from malignancy on PET is difficult. Some researchers have suggested that the SUV value of ≥ 13 is more specific for malignancy, especially for aggressive lymphomas. In our first patient, the FDG activity in the lymphoma foci (SUVmax 14.1) was indeed more intense than in tissues harboring sarcoidosis (SUVmax 7.8). However, sarcoid lesions can have SUVs approaching that of aggressive lymphoma, and FDF uptake intensity alone should not be regarded reliable in distinction [4,14,15]. On the other hand, the pattern of FDF uptake may provide clues for differentiation: streaky and dotted uptake characterizes sarcoid myopathy while homogeneous uptake is a feature of lymphoma. However, this distinction is not definitive, and early stage disease might not present with a typical uptake pattern. Therefore, PET is of limited utility in distinguishing sarcoidosis from lymphoma.

MRI is currently the most useful image modality to distinguish sarcoid myopathy from muscular lymphoma. Nodular type sarcoid myopathy usually shows high signal intensity on T2-weighted images and presents with rim enhancement on contrast-enhanced

images. The "dark star" and the "3 stripes" signs are typical patterns found on T2-weighted or contrast-enhanced T1-weighted images, in axial and coronal views, respectively. These signs correspond to the lesion's rim-enhancing nature, and reflect the fibrotic center resulting from longstanding inflammation with surrounding active granulomatous inflammation [8, 16,17]. The MRI of our first patient's thighs was consistent with nodular type muscular sarcoidosis, and the diagnosis was confirmed by a histological study. Conversely, lymphoma of the skeletal muscle usually shows muscular enlargement due to the presence of soft tissue mass, and is iso- to hyperintense on T1- and T2-weighted images. They usually demonstrate homogeneous gadolinium enhancement [18,19]. Our second patient had prominent enlargement of the left hamstring muscles on MRI, with homogenous but mild gadolinium enhancement. After six cycles of R-CHOP chemotherapy, the intramuscular mass resolved with only faint residual contrast enhancement.

In summary, we have presented a case of concomitant muscular sarcoidosis and DLBCL of the nasopharynx and a case of primary skeletal muscle DLBCL. Both muscular sarcoidosis and muscular lymphoma show high FDG uptake, and is difficult to differentiate on a PET scan alone. MRI may provide valuable information in differentiating these two entities, and has the advantage of being noninvasive and free of radiation. However, when suspicious lesions develop in a patient with known sarcoidosis, or in situations where PET shows an unusual involvement pattern in a patient with lymphoma, histological verification is still recommended, especially when the treatment decision relies on a confirmative diagnosis.

REFERENCES

1. Brincker H. The sarcoidosis-lymphoma syndrome. **Br J Cancer 54:** 467-473, 1986.
2. Karakantza M, MacLennan K, O'Connor NT, et al. Association between sarcoidosis and lymphoma revisited. **J Clin Pathol 49:** 208-212, 1996.
3. Sobic-Saranovic D, Artiko V, Obradovic V. FDG PET imaging in sarcoidosis. **Semin Nucl Med 43:** 404-411, 2013.
4. Goswami T, Siddique S, Cohen P, et al. The Sarcoid-lymphoma syndrome. **Clin Lymphoma Myeloma Leuk 10:** 241-247, 2010.
5. Resnick D NG. Sarcoidosis. In: Resnick D NG (ed) Diagnosis of bone and joint disorders 3rd ed. Saunders, Philadelphia, Pa, pp. 4333-4352, 1995.
6. Otake S, Ishigaki T. Muscular Sarcoidosis. **Semin Musculoskelet Radiol 05:** 167-170, 2001.
7. Zisman DA, Biermann JS, Martinez FJ, et al. Sarcoidosis resenting as a tumorlike muscular lesion. Case report and review of the literature. **Medicine 78:** 112-122, 1999.
8. Otake S. Sarcoidosis involving skeletal muscle: imaging findings and relative value of imaging procedures. **AJR Am J Roentgenol 162:** 369- 375, 1994.
9. Wolfe SM, Aelion JA, Goodman RE. Myopathy in sarcoidosis: clinical and pathologic study of four cases and review of the literature. **Semin Arthritis Rheum 16:** 300-306, 1987.
10. Glass AG, Karnell LH, Menck HR. The national cancer data base report on non-hodgkin's lymphoma. **Cancer 80:** 2311-2320, 1997.
11. Samuel LM, White J, Lessells AM, et al. Primary non-Hodgkin's lymphoma of muscle. **Clin Oncol 11:** 49-51, 1999.
12. WieÎrs G, Lhommel R, Lecouvet F, et al. A tiger man. **Lancet 380:** 1859, 2012.
13. Soussan M, Augier A, Brillet PY, et al. Functional imaging in extrapulmonary sarcoidosis: FDG-PET/CT and MR features. **Clin Nucl Med 39:** e146-59, 2013.
14. Schöder H, Noy A, Gönen M, et al. Intensity of 18-fluorodeoxyglucose uptake in positron emission tomography distinguishes between indolent and aggressive non-Hodgkin's lymphoma. **J Clin Oncol 23:** 4643-4651, 2005.
15. Rodriguez M, Rehn S, Ahlström H, et al. Predict-

ing malignancy frade with PET in non-Hodgkin's lymphoma. **J Nucl Med 36:** 1790-1796, 1995.

16. Sekine T, Amano Y, Hidaka F, et al. Hepatosplenic and muscular sarcoidosis: characterization with MR imaging. **Magn Reson Med Sci 11:** 83-89, 2012.
17. Moore SL, Teirstein A, Golimbu C. MRI of sarcoidosis patients with musculoskeletal symptoms. **AJR Am J Roentgenol 185:** 154-159, 2005.
18. Suresh S, Saifuddin A, O'Donnell P. Lymphoma presenting as a musculoskeletal soft tissue mass: MRI findings in 24 cases. **Eur Radiol 18:** 2628-2634, 2008.
19. Chun CW, Jee WH, Park HJ, et al. MRI features of skeletal muscle lymphoma. **AJR Am J Roentgenol 195:** 1355-1360, 2010.